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SWITZER, JULIET CAROLINE	
ART UNIT	**PAPER NUMBER**
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/727,576	SHARMA ET AL.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 18-35 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 18-35 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The papers filed 3/5/07 have been considered, but are not sufficient to place the application in condition for allowance for the reasons set forth in this office action. A full statement of the rejections is set forth and then a response to applicant's remarks. Any rejection not reiterated in this office action was overcome by applicant's amendments to the claims. **This action is FINAL.**

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 18-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a rejection for new matter. The pending claims were filed in an amendment on 3/5/07.

The newly filed claims include the limitation that mRNA is isolated from blood cells from a patient having cancer wherein said cells (which are from blood) "have not contacted the area of said cancer." All of the independent claims contain similar limitations, reciting the mRNA isolated from blood cells from a patient with cancer wherein the blood has not contacted the area of the cancer. This particular combination of limitations does not appear to have basis in the parent specification. Namely, the specification does not provide basis for blood cells in a

patient with cancer wherein the blood cells have not contacted the area of disease, and in particular where the cancer is breast cancer.

Therefore, the claims are rejected as containing new matter.

Claim Rejections - 35 USC § 112

4. Claims 18-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of the Invention

The invention concerns identifying and using isolated selected mRNA species or cDNA species that are "useful for diagnosing or identifying breast cancer." The claims include claims directed to methods of obtaining isolated selected mRNA species "useful for diagnosing or identifying breast cancer," and methods for preparing a gene transcript pattern probe kit which comprise steps of isolating mRNA from cells from blood of more than one human who are known to have breast cancer (for example, independent claims 18 and 19). The claims require that the cells "have not contacted the area of said breast cancer." The further method steps of these claims set forth isolating mRNA from cells from a normal sample, and separating the mRNA species and selecting 10 or more mRNA he claims are also drawn to methods for diagnosing patients using said the products identified by the methods for obtaining isolated selected mRNA species.

Additional claims are drawn to methods for preparing a standard gene transcript pattern characteristic of breast cancer and include steps where blood cells from an human known to have

cancer is obtained and mRNA is isolated, and the mRNA is hybridized to mRNAs which are present "at a different level" in a blood sample from one or more normal patients versus patients with cancer, wherein the mRNA are "specific for said breast cancer" and wherein said cells have not contacted the area of said breast cancer (for example, independent claims 27 and 28). Thus, in this case the nature of the invention requires the knowledge of which particular transcripts meet the characteristics that they are expressed at different levels in blood that has not contacted the area of said cancer. The claims set forth that the methods will isolate nucleic acids that are "useful for diagnosing or identifying breast cancer" and thus the nature of the invention also requires that the disclosed methods identify such molecules reliably such that they can be used in diagnosing or identifying breast cancer. The claims are all related to the identification and use of mRNA species that are present at different levels in breast cancer versus non-cancer samples.

Independent claim 29 is drawn to a method "of diagnosing or identifying breast cancer" and has steps where a standard gene transcript pattern is produced for a test sample (steps (a) to (c) which are similar to steps (a) to (c) of claims 27 and 28) and then this pattern is compared to a pattern which is produced from an individual who is known to have said breast cancer. The claim recites that the comparison is carried out "so as to determine the degree of correlation indicative of the presence of said breast cancer, and so as to diagnose or identify said breast cancer." Thus, in this case the nature of the invention requires the knowledge of which particular transcripts meet the characteristics that they are expressed at different levels in blood that has not contacted the area of said breast cancer.

In summary, independent claims 18 and 19 are methods for identifying differentially expressed transcripts which are useful for diagnosing, identifying or staging cancer, while claims

27, 28, and 29 make use of these transcripts for preparing transcript patterns and for diagnosing, or identifying breast cancer. In all cases the claims recite analysis of mRNA from blood cells that have not come in contact with the cancer. Furthermore, in all cases, the claims rely upon the ability to associate the presence of mRNA at "different levels" in control and cancer patients with the diagnosis or indication of cancer.

Scope of the claims

The independent claims are all sufficiently broad so as to encompass the obtaining or use of any possible 10 or more molecules for the "diagnosing or identifying breast cancer." The claims are broad in scope with regard to the fact that in all of the claims the critical molecules are entirely unidentified. The claims are very broad in scope because they encompass finding or using molecules related to any type of breast cancer, which includes invasive breast cancer, for example invasive ductal or lobular carcinomas as well as in situ breast cancers, inflammatory breast cancer, medullary carcinoma, mucinous carcinoma, Paget's disease of the breast, tubular carcinoma, phylloides tumor, metaplastic carcinoma, sarcoma, etc. The claims are also extremely broad because they require only the comparison of a mRNA levels in a as few as two individuals' blood to that of as few as two other individuals, and the claims thus imply that the difference in such small groups of peoples' levels of mRNA expression is sufficient to identify a molecule as a marker and use that molecule in diagnostic procedures.

The requirement in the claims that the test blood cells "have not contacted the area of said breast cancer" significantly narrows the scope of the claims with regard to this aspect, since blood flow is generally known to carry blood throughout organisms, and this limitation requires examining blood cells that have not contacted certain portions of the body.

Teachings in the Specification/Examples

The specification does not provide a single working example of methods which are applied to breast cancer in humans. The specification generally discusses that the disclosed methods can be applied to cancer (p. 6, 2nd ¶), but not a single working example is provided where nucleic acids which would be useful for diagnosing or identifying breast cancer are actually obtained, nor does the specification provide an example of where such molecules are used to diagnose or identify breast cancer.

The specification does not provide any guidance as to how to identify blood cells within a blood sample that have or have not come in contact with a particular part of the body. The claims are limited so as to be related only to breast cancer, so presumably in this case the cancer would be at least in the breast (but obviously could be other places throughout the body if there had been metastases). The specification does not provide any guidance as to how to identify blood cells which "have not contacted the area of disease."

The specification provides a single working example wherein mRNA is isolated from cells that did not come in contact with an area of disease and were obtained from an area distant from the area of disease is isolated and used to create diagnostic gene transcript patterns. Particularly, in example 6, a differential expression type methodology is used to analyze infection for a fungal pathogen in Norway spruce. A root fungus, Pythium dimorphum, is introduced to Norwegian spruce. Samples mRNA is collected from samples of the needles of the infected plants and control plants, reverse transcribed and amplified using primers specific to transcripts that were differentially expressed in plants that were infected with the fungus or spruce that were challenged with "other types of stress (specification page 38)." The amplified

cDNA samples were hybridized to probes for the differentially expressed transcripts. Hybridization patterns are shown in figure 2, where there is a clear difference in the pattern from the needles of the tree stressed with the fungus versus the control needles (see second page of Figure 2, bottom two graphs). However, this example does not sufficiently demonstrate that this method is diagnostic of the particular condition of the fungal pathogen, because it does not differentiate between the determination that one can determine that the spruce was STRESSED versus having a particular disease. The example states that some of the probes used are not specific to the disease but of are particular to stressed plants.

The remaining examples provided in the specification are largely prophetic, and do not provide clear data which indicates the functionality of this invention for cancer or any other disease. Examples 1 and 2 provide direction as to the use of this invention for the diagnosis of Alzheimer's disease and senile dementia, however, they do not provide the transcript patterns necessary or any specific probes useful for the diagnosis. Example 4 appears to provide the use of a differential expression methodology for the production of a diagnostic transcript pattern for Arabidopsis, however, the specification does not provide any data as to the disease being studied. Thus, it is unclear if the disease is systemic or localized. It is not clear if the tissue samples taken were from the location of the disease or from some other disease. The example states that it is leaves that are sampled, but it gives no indication if it was healthy leaves or diseased leaves. Example 5 provides a prophetic example of humans, merely stating that results would be expected to be "similar to those in figure 1." The result in figure 1 appear to be hypothetical results.

State of the Prior Art and Level of Unpredictablity

The prior art provides extensive guidance as to the use of differential expression methodology for the identification of probes useful for the detection of disease (see, for example, Graber *et al.* or Ditkoff *et al.*, as cited in the IDS). With regard to the identification of nucleic acid probes which are isolated from cells have not come in contact with the area of the cancer, the prior art is silent. Ralph *et al.* (US 6190857, as cited in IDS) provide probes which identify genes that are expressed in the peripheral blood of individuals with prostate or breast cancer compared to normal individuals. Ralph et al. teach that their invention is directed towards detecting a response of circulating leukocytes to the disease site (Col. 5), thus suggesting that the basis of their invention is that the cells have in fact come in contact with the disease site. Zhi-Xin *et al.* (as cited in IDS) teach that IL-2R expression in peripheral blood mononuclear cells is closely associated with the presence of tumor metastasis in lung cancer patients. Like Ralph et al., Zhi-Xin et al. teach that the expression they are detecting is a result of the cells coming in contact with the cancer cells (see page 10 of the translation of Zhi-Xin et al).

Neither the specification nor the prior art provide any guidance as to how to identify cells in a blood sample that have "not come in contact with the area of said cancer." For example, the specification does not provide any guidance as to how one would ascertain which blood cells in a sample have come in contact with the "area" of the possible breast tumor and which have not. This identification is highly unpredictable since they would ostensibly all cells be in the same blood sample. Liew et al. (J Lab Clin Med 2006; 147:126-132) teach that "Blood is classified as a fluid connective tissue which can be defined as cells suspended in a fluid matrix functioning to connect the entire biological system at the physiological level...Thus, the blood pervades the entire body, is in a constant state of renewal, and provides a protective barrier

between the external and internal environments (p. 126)." Simply put, blood travels throughout the entire organism, and it is unknown how one would identify blood cells that have or have not come in contact with "the area of said breast cancer" if that cancer is a tumor of the breast or even breast cancer which has metastasized to other parts of the body, including, commonly, lymph nodes.

While level of skill in the art is quite high, but the unpredictability associated with identifying isolated selected mRNA species which are obtained from cells which have not contacted the point of cancer and are useful for the detection of cancer is higher. The human blood, for example, expresses hundreds of thousands of different transcripts, and which of these particular transcripts would be useful for the detection of any particular disease is highly unpredictable. The determination of such an association requires extensive laboratory work, as is exemplified by the teachings of Ralph *et al.* In order to enable the instant claims to their current breadth, some showing that the method functions for a representative number of types of breast cancer would be required. Since the claims embrace diagnostics for any type and stage of breast cancer, a representative number would have to include a variety of different breast cancer types. No such showing is provided in the instant specification.

Further, the claims of the instant application set forth the comparison of the mRNA or cDNA levels in as few as two individuals versus another group of as few as two indiviuals, and they suggest or overtly claim that a difference in gene expression between the two sufficent to identify or diagnose breast cancer. Neither the specificaiton nor the claims, for any individual gene or for all genes in general, set forth a threshold of difference between two individuals that would be sufficient to conclude that the difference in gene expression between a test individual

and any control individual (either with or without cancer) is sufficient to draw this conclusion. Because the claims encompass any level of altered gene expression, it is relevant to point out that the post-filing art of Cheung et al (2003, Nature Genetics, Vol. 33, 422-425) teaches that there is natural variation in gene expression among different individuals. The reference teaches an assessment of natural variation of gene expression in lymphoblastoid cells in humans, and analyzes the variation of expression data among individuals and within individuals (replicates) (p.422, last paragraph; Fig 1). The data indicates that, for example, expression of ACTG2 in 35 individuals varied by a factor of 17; and that in expression of the 40 genes with the highest variance ratios, the highest and lowest values differed by a factor of 2.4 or greater (Fig 3). It is thus unpredictable as to whether or not any level of altered gene expression is indicative of a disease.

The unpredictability of correlating gene expression level to any phenotypic quality is taught in the post-filing art of Wu (2001, J Pathol 195:53-65). Wu teaches that gene expression data, such as microarray data, must be interpreted in the context of other biological knowledge, involving various types of 'post genomics' informatics, including gene networks, gene pathways, and gene ontologies (p.53, left col.). The reference indicates that many factors may be influential to the outcome of data analysis, and teaches that expression data can be interpreted in many ways. The conclusions that can be drawn from a given set of data depend heavily on the particular choice of data analysis. Much of the data analysis depends on such low-level considerations as normalization and such basic assumptions as normality (p.63 - Discussion). The art of Newton et al (2001, Journal of Computational Biology, Vol. 8, No. 1, pages 37-52) further teaches the difficulty in applying gene expression results. Newton et al teaches that a

basic statistical problem is determining when the measured differential expression is likely to reflect a real biological shift in gene expression, and replication of data is critical to validation (p.38, third full paragraph).

Quantity of Experimentation

The instant specification does not provide enabling support for the practice of a single embodiment within the claimed invention. An extensive amount of experimentation would be required to practice the claimed invention. First, one would be required to establish methodology to determine if particular blood cells have come in contact with an area of breast cancer. This in itself is a highly unpredictible endeavour, if not impossible, given that blood travels throughout the entire body. Further, though, given the broad scope of the claims and the unpredictable nature of the invention, one would have to also undertake extensive experimentation to establish whether ten or more markers can be identified in the blood as differentially expressed in patients having any single type of breast cancer, and also whether these markers are specific to the type of breast cancer or if they are common markers for all breast cancers. One would have to complete this experimentation using case controlled studies for many, many types of cancer, including htose recited in claims 37 and 38, but also for others in order to meet the scope of the instant claims. The markers used in the methods for diagnosis in the instant claims are entirely undefined by the specificaiton by any structural means, and thus, one would have to undertake the discovery of these molecules for each type of breast cancer one wanted to practice the claimed invention in order to diagnose or identify. The

quantity of experimentaiton, especially in view of the unpredictable nature of the invention, is enormous.

Conclusion

Thus, having carefully considered all of these factors, it is concluded that it would require undue experimentaiton to practice the claimed invention.

5. Claims 27-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Independent claims 27, 28, and 29 each include steps wherein isolated mRNA or isolated cDNA from a sample are hybridized to 10 or more mRNA or cDNA species transcribed from mRNA which are present at a different level in cells in a blood sample from one or more normal humans than in corresponding cells in a blood sample from one or more eukaryotic organisms known to have said breast cancer. The claim further requires that the 10 or more mRNA are "specific" for said breast cancer and that the cells in which they are differentially expressed have not contacted the area of said breast cancer and that the blood sample is obtained from a part of said organism distant to the area of said cancer. Thus, the practice of the claimed method requires the hybridization to a particular set of probes that are identified only by their function (that they are differentially present in two samples and that they are indicative of cancer) and by the type of cell that they were identified within (blood cells that have not touched the area of the disease and that were isolated distant from the area of disease). The specification and claims

suggest that there are hundreds of possible genes that meet these requirements (see claim 34, for example which requires that between 10 and 500 mRNA species are used). The scope of the claim is thus quite broad with regard to the actual sequences used. There are thousands of possible genes within the genome of any given eukaryotic organism.

The application does not provide any descriptive support of even a single example of an appropriate mRNA or cDNA probe for use in the claimed methods. The specification generally suggests that such probes could be identified for cancer, but does not describe a single sequence that falls within the scope of the requirements for sequences in step (b) of the rejected independent claims. Thus, there is no actual reduction to practice. There is no detailed drawing or chemical formula or even gene name to suggest molecules that would be useful in the claimed invention. There is no disclosure of sufficient, relevant, identifying characteristics of the molecules essential to practice the claimed invention, other than a general disclosure of their function. The specifically generally suggests such molecules as are necessary to practice the claimed invention might exist, but the specification does not provide any written description as to what the structure of these molecules is. Thus, the claims are rejected for lack of adequate written description.

Double Patenting

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re*

Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 18-38 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-36 of copending Application No. 11/149370. Although the conflicting claims are not identical, they are not patentably distinct from each other because the independent claims in the copending application require steps that are generic to the instantly claimed invention since the independent claims in the copending application encompass methods relative to any disease. These claims do have very similar steps to those in the instant invention, namely they specifically recite blood cells that are obtained from a part of said human distant to the area of disease and have not contacted said area of said disease. Likewise, each of the limitations of the dependent claims in the instant application are provided in dependent claims in the copending application. Claims 35 and 36 recite embodiments wherein said disease is "cancer" and wherein said disease is "stomach, lung, breast, prostate, and bowel cancer." Thus, given all of these recitations, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have practiced the methods set forth in the copending application and applied those methods to cancer, and more particularly any or all of the cancer types recited in the claims of the copending application, including breast cancer. One would have been motivated to practice such an invention by the express presence of these embodiments as claimed embodiments.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Remarks

Applicant traverses the rejection for new matter and lack of enablement beginning on page 14 of the response.

Applicant first points out that the scope of the claims has been limited to "breast cancer" and "humans" and to set forth that blood from "more than one" individuals is used. The rejection has been modified to address these amendments.

Applicant points out that the specification contains reference to using blood samples for cancer detection at page 6, second paragraph, which states that diseases which result in metabolic or physiological changes include breast cancer, and page 7, three lines from the bottom which states that "tissue" samples include "blood," and page 23 which states that the diagnostic method of the invention may be used to identify cancer in humans and that "body parts distant from the site of interest, e.g. a tumour may be analysed..." This clearly establishes written description for the use of blood as the tissue sample in the claimed methods. None of these establish that the blood has not contacted the "area of said breast cancer" commensurate in scope with the instant claims.

Applicant points out that example 1 discloses the use of a blood sample for the diagnosis of Alzheimer syndrome, wherein in this case "the area of disease" is ostensibly the brain, and peripheral blood will not have crossed the blood brain barrier. However, this example does not provide basis for drawing blood that has not contacted the "area of disease" of breast cancer,

which "area of disease" includes, for example, breast tissue in general, or lymph nodes, or other body parts which ARE NOT surrounded by a blood-brain barrier. The specific example of Alzheimer's disease is not a general example that provides written description for any claim where the blood has not contacted the "area of disease." Furthermore, applicant's remarks are confusing because applicant appears to be attempting to establish basis for the instantly claimed invention in the specification but very clearly states in the final full sentence of the third paragraph on page 14 of the remarks that "the specification does **not** contemplate using blood samples where the blood cells have not contacted the site of the disease (emphasis added)."

Applicant points out that page 10 of the specification refers to the whole organism responding to a changed condition in the presence of disease and that the effects can be observed on body parts distant from the site of interest. However, neither of these citations set forth that this occurs when blood has not contacted the "area of disease" of breast cancer, and area, in this case, which includes breast tissue at least and potentially any other tissue, including the blood itself, which has metastatic cells present. Applicant points to page 11 which refers to early diagnosis before other symptoms appear. This is very different from referring to the ability to identify markers- that is screen for and select the markers that MIGHT be useful for diagnosis- early before symptoms appear.

On page 14 in the fourth full paragraph applicant begins a discussion of in situ tumors where the tumor has not yet penetrated the basement membrane of the blood vessel, and thus the circulating blood cells would not have come in contact with the tumor. First, it is to be clearly noted that the instant application provides no specific discussion of breast cancer beyond general recitations that the methods of the instant specification can be applied to "breast cancer." The

specification does not discuss in situ versus invasive cancers, and never contemplates methods which examine and diagnose any particular subset of breast cancers. Further, Applicant's arguments rely on a very narrow interpretation of the "area of disease" with regard to the instant claims which recite breast cancer. A reasonable interpretation of this phrase includes, for example breast tissue, but even include any tissue outside the breast where disease may have spread. Some might even include the entire "upper body" as the "area of disease" relative to the legs, for example. Applicant's remarks focus on the "area of disease" as being cancer cells themselves, a much more limited definition. To exclude the "breast" from the scope of the "area of disease" for "breast cancer" is to simply read a much narrower interpretation of the claim than in currently set forth.

Applicant's specific arguments which are limited to in situ breast cancers simply focus on one particular embodiment within the scope of the claims, an embodiment which is neither claimed in the claims, nor ever specifically discussed in the specification. Applicants state that the provided references (p. 14-15) show that it was known as of applicant's priority date to isolate blood that has not come in contact with a breast cancer. In the case of in situ cancers, it may have been known as of the filing date that these cancers have not penetrated the circulatory system, but this is not the same as stating the one knew how to take a sample of blood that "has not come in contact with the area of disease" when blood is known to travel throughout the body and wash over all tissues. Even if the blood did not touch a tumor cell, the cells themselves are producing metabolites which are released into body fluids and which may or may not come in contact with the blood. Patients having a particular type of breast cancer in which the tumor has not come in contact with the blood may be able to be identified by mammogram, but even in

these cases there is no sure way of knowing whether single cells have infiltrated the circulatory system or not. Either way, it is reiterated that the scope of the claim is sufficiently broad so as to refer to ALL types of breast cancer and to require that the blood has not come in contact with "the area of said breast cancer" which includes not only the tumor, but reasonably includes the breast itself.

Applicants provide details and experimental data as an appendix to the remarks. These data are considered only as attorney's arguments since they are not in declaration form. Attorney arguments cannot replace evidence on the record. The description of the experiment does not establish the isolation of blood that has not come in contact with the breast. Furthermore, it is noted that total RNA was extracted from blood samples, cDNA probes were prepared and the probes were hybridized to arrays to determine differentially expressed genes. This is not the method described in the instant specification, which in fact teaches away from using hybridization to preselected probes for the identification of the markers according to the claimed invention. Namely, when discussing separation of the cDNA within a sample for comparison to another sample to identify differentially expressed transcripts, the specification teaches that "Sequence based separation techniques, which are excluded, include for example capture with probes directed to different sequences by hybridization or sequencing itself..." further teaching that methods which are not sequence based offer the advantage that "probes to be used in the methods of the invention are identified and selected from the entire population of transcripts or cDNA since no selection is made on the basis of their sequence before separation...Thus the identification of the transcripts is not biased towards the selection of particular transcripts from a subset of total transcripts (specification page 13). Applicant is further reminded to review the

criteria for timeliness of an affidavit or declaration prior to further filings in this application (MPEP 716.01). The rejections for new matter and lack of enablement are MAINTAINED.

Regarding the written description rejection applicant states that the claims have been limited to humans and breast cancer thus reducing the total number of genes from which to choose. However, although there are fewer genes to choose from now that the claims are limited to humans, there are still on the order of tens of thousands of possible genes in the human genome many with multiple transcripts, and so the scope of the claims remains extremely broad. The rejection is maintained.

The double patenting rejection is maintained. No arguments were presented to traverse the rejection.

Conclusion

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday, Tuesday, or Thursday, from 9:00 AM until 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached by calling (571) 272-0735.

The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

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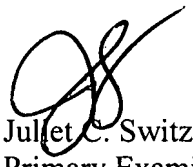

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